(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number : **0 338 861 B1**

(12) # EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification : **20.01.93 Bulletin 93/03**

(51) Int. Cl.[5] : **A61K 9/26,** A61K 33/08

(21) Application number : **89304013.9**

(22) Date of filing : **21.04.89**

(54) **Antacid compositions with prolonged gastric residence time.**

The file contains technical information submitted after the application was filed and not included in this specification

(30) Priority : **21.04.88 GB 8809421**

(43) Date of publication of application : **25.10.89 Bulletin 89/43**

(45) Publication of the grant of the patent : **20.01.93 Bulletin 93/03**

(84) Designated Contracting States : **AT BE CH DE ES FR GB GR IT LI LU NL SE**

(56) References cited :
EP-A- 0 093 538
EP-A- 0 227 603
FR-A- 1 416 304
FR-A- 2 092 107
US-A- 4 199 560
US-A- 4 605 551

(73) Proprietor : **WALTON S.A.**
Avenida Santiago de Compostela no. 60 7o. A
Madrid (ES)

(72) Inventor : **Spickett, Robert Geoffrey William**
Tibidabo 23
Barcelona (ES)
Inventor : **Vidal, Jose Luis Fabregas**
Dos de Mayo 327
Barcelona (ES)
Inventor : **Escoi, Juan Cucala**
Pintor Jose Pinos 16
Barcelona (ES)

(74) Representative : **Goldin, Douglas Michael et al**
J.A. KEMP & CO. 14, South Square Gray's Inn
London WC1R 5EU (GB)

EP 0 338 861 B1

Description

This invention relates to antacid compositions having a prolonged gastric residence time.

Classical antacids such as aluminium and magnesium hydroxide gels and co-gels and the new crystalline aluminium magnesium hydroxycarbonates or sulphates such as Hydrotalcite, Almagate and Magaldrate are either rapidly neutralized to water soluble ions or sediment in the fundus of the stomach, and are evacuated into the duodenum by normal peristalsis with subsequent loss of unused drug from its site of action. Consequently they do not neutralize the continuous output of hydrochloric acid by the parietal cells in the human stomach for a prolonged period of time.

US-A-4,199,560 relates to a solid oral pharmaceutical preparation with protracted release of the active ingredient consisting of discrete solid granules containing the active ingredient soluble in the stomach and auxiliary agents and of an equally solid external phase surrounding the said granules, whereby the granules forming the internal phase consist of granules prepared from a powder mixture which contains as active ingredient, or in addition to it a non toxic metal compound, being capable of binding an acid, and being insoluble or but slightly soluble in neutral aqueous medium particularly bismuth, aluminium or magnesium compound and auxiliary materials prepared with an aqueous emulsion containing a hydrophobic component and hydrophylic emulsifiers, and the external phase contains a solid dry, amphoteric gel forming substance in an amount of 1-50 percent w/w related to the total weight of the preparation in admixture with auxiliary agents.

The present invention provides solid oral pharmaceutical preparation with protracted action consisting of an internal phase of discrete solid granules containing the active antacid ingredient and a solid external phase surrounding the said granules. The internal phase consists of a powder mixture containing the active antacid ingredient and pharmaceutically acceptable excipients and the external phase contains a hydrophobic organic substance, particularly stearic, or palmitic acid esters, a hydroxylated polyalkene polymer and a non-ionic emulsifier.

The preparations described in this invention do not sediment to the fundus of the stomach, are more slowly evacuated to the duodenum by peristalsis and are available in the stomach to neutralise the hydrochloric acid secreted by the parietal cells for a prolonged period of time, and consequently resolve an important problem in the field of antacid therapy.

It is well known that hyperacidity alone does not cause ulcers, but can be a factor in their formation, and can also inhibit healing of preformed ulcers. However, it is desirable that hyperacidity be reduced and an antacid should satisfy the following criteria:

- The neutralizing effect must be rapid and maintained during normal digestion time in the stomach.
- It must neutralise the required amount of acid.
- It must raise the pH value of the gastric contents to a level at which pepsin activity is reduced but not fully inhibited.
- It should not cause the gastric pH to rise above 6.
- It should not cause systemic alkalosis even when administered repeatedly.
- The antacid should not be emptied into the duodenum until it has exerted its full effect in the stomach.

The present invention includes two-phase solid oral pharmaceutical compositions: e.g. in the form of powder, tablets (effervescent, chewable), coated tablets or capsules, with prolonged antacid activity. The composition may be prepared by granulation of a powder mixture containing the active antacid ingredient, a solid carrier and other excipients with an organic emulsion containing hydrophobic and hydrophilic components, to form granules surrounded by an external phase which, owing to its specific physico-chemical properties, prolongs the liberation of the active ingredient thereby augmenting its biological utilization. The resulting granules can then be tableted or filled into capsules. The granulating emulsion may contain as hydrophobic component, for example, esters of 12-hydroxystearic, stearic, or palmitic acid and, as hydrophilic component, a hydroxylated polyalkene polymer. By appropriate selection of the components of the emulsion, particularly the non-ionic surface active agent, e.g.polyoxyethylene sorbitan esters and changing their quantitative ratio, the rate of liberation and gastric residence time of the active ingredient can be modified.

More specifically this invention provides compositions of products with antacid properties in which the active component is a crystalline synthetic antacid such as Almagate, Hydrotalcite, Magaldrate; the compositions may also contain aluminium hydroxide or aluminium magnesium hydroxide cogels, in a vehicle which provides a prolonged gastric residence time. The prolonged residence time is a function of the lipophilicity of the particles which preferentially adhere to the gastric mucosa or form a layer on the surface of the gastric contents. The antacid is then slowly liberated, reacts with hydrogen ions in the vicinity, protects the mucosa and its emptying from the stomach is delayed in spite of peristaltic movements. The invention involves coating the particles of the antacid product with a solid emulsion of selected excipients, which increases the lipophilicity and delays reaction with hydrogen ions without altering the intrinsic acid neutralising properties.

The hydrophilic component of the emulsion can be a hydroxylated polyalkene polymer, with molecular weight 950-10.000, preferably 5000-7000, and the hydrophobic component can be glycerol mono-, di- or tripalmitic or stearic esters, or preferably hydrogenated mono-, di- or triglycerides, especially those containing 70-90% of 12-hydroxystearic acid esters and 10-30% of stearic acid esters. A non-ionic surface active agent, suitable for use with water in oil emulsions can be used as an emulsion stabiliser. The selection of the optimal composition for delaying active ingredient liberation and increasing gastric residence time may be calculated from the hydrophilic-lipophilic balance (HLB) of the components of the granulating emulsion. Non-ionic emulsifiers such as polyoxy-ethylene -sorbitan-monooleates, polyoxyethylene-sorbitan-monolaurates, polyoxyethylene-sorbitan-monostearates and monopalmitates, and preferably sorbitan fatty acid esters (lauric, palmitic, oleic) with a hydrophilic-lipophilic balance lower than 7, generally give satisfactory results if the amount of the hydrophobic component emulsified in the granulating liquid is between 50-90 parts, preferably 80 parts by weight and the hydrophilic component is between 10-20, preferably 13 parts by weight. Such granulating emulsions are expediently prepared by dissolving the hydrophobic component in a convenient amount of chloroform or methylene chloride warming to 30 C, adding the emulsifier to the solution thus obtained, and emulsifying with the hydrophilic compound.

The resulting granulating emulsion can then be used for granulating the powder mixture containing active ingredients, carrier, and optionally other excipients. For example, one part by weight of the powder mixture is admixed and kneaded, preferably with 1 to 3 parts by weight of granulating emulsion. The wet mass, is kneaded again with a solution of a binder e.g. gelatin, polyvinylpyrrolidone, hydroxypropylcellulose, preferably an aqueous 3% solution of polyvinylpyrrolidone, and finally the wet mass granulated by known methods e.g. by pressing through a sieve. Flavouring substances, disintegrants and lubricating agents, such as cross-linked sodium carboxymethylcellulose and magnesium stearate, can then be added to the dried granules and the mixture pressed into tablets or filled into bottles, individual sachets or hard gelatin capsules.

The preferred pharmaceutical forms for utilization of the preparation of this invention are powders, granulates, or chewable tablets, which may or may not be combined with an adequate amount of uncoated active component to ensure a rapid initial acid neutralization. The dose of antacid (uncoated and coated) should be sufficient to neutralize the acid output of the parietal cell over a prolonged time period by limiting the loss of unused antacid by periodic gastric emptying. With conventional antacids this would only be possible with high doses of the active principles causing gastric pH to rise above 6. In addition loss of unchanged antacid by normal peristalsis into the duodenum where its presence is either not required or unwanted reduces their clinical utility.

The present invention provides:

1) The possibility of administration of higher, and more efficacious doses of antacid with longer intervals between doses.

2) Physical protection of the gastric mucosa against fluctuations of pH.

3) Prolonged antacid effect, favouring patient comfort and compliance.

4) More complete utilization of the adminstered dose by prolonged residence time in the stomach.

5) Reduction of gastro-oesophageal acid reflux due to the presence of a reserve of floating antacid on the surface of the gastric contents.

In an additional aspect of this invention the above compositions may be combined with substances which inhibit gastric acid secretion, e.g., cimetidine, ranitidine or other H_2-antihistamines or proton pump blockers for the treatment of gastrooesophageal reflux disease and gastroduodenal ulcers.

Further details of the present invention are to be found in the following Examples without limiting the scope of the claims to the Examples.

EXAMPLE 1

For the production of a granulate preparation with floating and protracted dissolution properties the following quantities of substances are used per gram of final product:

Hydrotalcite	0,75 g
Hydrophobic silicon dioxide	0.14 g
Sorbitan monooleate 60	0.005 g
Polyoxyethylene stearate	0.01 g
Castorwax	0.06 g
Polyvinylpyrrolidone	0.035 g

The hydrotalcite and hydrophobic silicon dioxide are milled to a particle diameter less than 125 µm, (very fine powder) and are mixed to form a homogeneous mixture, then kneaded successively with granulating liquids A and B prepared as follows:

Granulating liquid A:

Sorbitan monooleate, polyoxyethylene stearate, and castorwax are dissolved in warm (35°C) methylene chloride.

Granulating liquid B:

Polyvinylnyrrolidone is dissolved, with vigorous stirring in 96% by vol. ethyl alcohol, at room temperature.

The wet mass is passed through a sieve (no 14 ASTM), dried (60°C, air circulating oven), finishing and lubricating substances (e.g. magnesium stearate and Aerosil) are admixed, and the mixture is dosed into multidose plastic bottles.

Utilising the above process granulate preparations of almagate and magaldrate can be prepared containing 0.75 g of active principal per g. of granulate.

EXAMPLE 2

For the production of chewable tablets the following materials are used:

	Amount per tablet
Magaldrate	0.75 g
Silicon dioxide	0.14 g
Polysorbate 21	0.001 g
Sorbitan Monooleate 60	0.004 g
Polyethyleneglycol 400	0.02 g
Glycerine tripalmitate	0.06 g
Polyvinylpyrrolidone	0.06 g
Mannitol	0.97 g

A granulate is prepared as described in Example 1 and is then blended with an auxiliary granulate of mannitol, prepared conventionally using an aqueous solution of polyvinylpyrrolidone as granulating liquid, to improve the flow properties of the powder. The mass is lubricated with e.g magnesium stearate and tablets are produced in conventional tableting equipment.

Utilising the above process tablets containing 0.75 g of almagate or hydrotalcite can be prepared.

EXAMPLE 3

Chewable tablets containing coated and uncoated antacid are prepared using the following materials:

	Amount per tablet
Almagate (antacid)	1.5 g
Hydrophobic silicon dioxide	0.14 g
Sorbitan Monooleate 60	0.005 g
Polyethyleneglycol 6000	0.01 g
Glycerol-tris-12-hydroxystearate	0.06 g
Mannitol	1.45 g
Potato starch	0.04 g
Polyvinylpyrrolidone	0.09 g

A mixture of a portion of antacid (between 50% and 70%) is mixed with the hydrophobic silicon dioxide and granulated as described in Example 1. The remainder of the antacid (up to 30%-50% of total amount) is blended with an equal weight of mannitol, potato starch is added, and the mixture is kneaded using a 6% aqueous solution of polyvinylpyrrolidone as granulating liquid.

The two granulates are mixed with a granulate of mannitol prepared as described in Example 2, flavour and lubricating agents are added, and the product is finally pressed into chewable tablets.

Utilising the above process tablets containing 1.5 g of hydrotalcite or magaldrate can be prepared.

The long lasting antacid effect of these preparations has been demonstrated by a modification of Fordran's test (Fordtran, J.S., Morawski, S.G., Richardson, C.T., New Engl. J. Med. 288, 923 (1973)) comparing the pure antacid with the formulations using the same amount of antacid in each case.

The modification consists of delaying the time of the first addition of gastric juice until the pharmaceutical composition had spontaneously disintegrated in a volume of up to 15 ml of distilled water. At this point the addition of synthetic gastric juice was commenced.

In this test the following results were obtained:

	Pure Almagate	Tablets prepared according to Example 3
Sample Weight	1.5 g	3.295g (equivalent to 1.5 g of Almagate)
pH at 10 min (after the first addition of 150 ml gastric juice)	4.70	4.98
Time above pH 3	68 min	115 min
Volume of HCL (0.079N) consumed	520.30 ml	527.02 ml

The coated product has a longer duration of action, i.e. a 1.7 times higher than that observed with the pure antacid.

The products of this invention have an "in vitro" bioavailability similar to that of the pure antacid, (Moragues, J., Beneyto, J.E., Fabregas, J.L., Spickett, R.G.W, Arzneim. Forsch., 34 (11), 10 a, 1346 (1984)).

The floating characteristics and prolonged gastric residence time with sustained acid neutralisation have been demonstrated in human volunteer studies using isotope labelled Almagate (scintigraphy).

In normal volunteers the time required for emptying 20% of the labelled antacid from the stomach is almost 3 times longer for coated Almagate than for the uncoated product. The latter empties with the liquid phase of a light standard meal whereas emptying of the former occurs much later with a half-life of 4 hours.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A solid pharmaceutical preparation having an internal phase which is a powder mixture of discrete solid granules of an antacid and a pharmaceutically acceptable excipient, the internal phase being surrounded by a solid external phase containing a hydrophobic organic substance, a hydroxylated polyalkene and a non ionic emulsifier.

2. A preparation according to claim 1, wherein the antacid is Almagate, Hydrotalcite, Magaldrate or other aluminium hydroxide or aluminium magnesium hydroxide gels.

3. A preparation according to claim 1 or 2, wherein the hydroxylated polyalkene has a molecular weight of 950 to 10,000.

4. A preparation according to any one of the preceding claims, wherein the hydrophobic organic substance is a glycerol mono-, di- or tri-ester of palmitic or stearic acid.

5. A preparation according to any one of the preceding claims, wherein the hydrophobic organic substance is a hydrogenated mono-, di- or tri-glyceride in which 70 - 90 per cent by weight of the ester is a 12-hydroxystearic ester and 10 - 30 per cent by weight of the ester is a stearic acid ester.

6. A preparation according to any one of the preceding claims, wherein the emulsifier is a polyoxyethylene-sorbitan mono-ester of an acid which is oleic, lauric, stearic or palmitic acid.

7. A preparation according to any one of the preceding claims additionally containing a gastric acid secretion inhibitor.

8. A preparation according to claim 7, wherein the inhibitor is cimetidine, ranitidine or omeprazole.

9. A preparation according to any one of the preceding claims in the form of a powder, granulate or chewable tablet.

10. A process for producing a preparation as defined in any one of the preceding claims which comprises forming an emulsion of the hydrophobic organic substance, the hydroxylated polyalkene and the emulsifier and then granulating a powder mixture containing the antacid and excipient with the emulsion.

11. A process according to claim 10, wherein the emulsion is formed by dissolving the hydrophobic substance in an organic solvent, adding the emulsifier to the resulting solution and then emulsifying the hydroxylated polyalkene into the mixture of solution and emulsifier.

12. A process according to claim 11, wherein the emulsion contains 50 - 90 parts by weight of the hydrophobic substance and 10 - 20 parts by weight of the hydroxylated polyalkene, the balance being solvent and emulsifier.

13. A process according to any one of claims 10 to 12, wherein 1 part by weight of the powder mixture is mixed and kneaded with 1 to 3 parts by weight of the emulsion, and a binder is then added to the resulting wet mass and the wet product finally granulated.

Claims for the following Contracting States : ES, GR

1. A process for producing a preparation of a solid pharmaceutical preparation having an internal phase which is a powder mixture of discrete solid granules of an antacid and a pharmaceutically acceptable excipient, the internal phase being surrounded by a solid external phase containing a hydrophobic organic substance, a hydroxylated polyalkene and a non-ionic emulsifier which comprises forming an emulsion of the hydrophobic organic substance, the hydroxylated polyalkene and the emulsifier and then granulating a powder mixture containing the antacid and excipient with the emulsion.

2. A process according to claim 1, wherein the antacid is Almagate, Hydrotalcite, Magaldrate or other aluminium hydroxide or aluminium magnesium hydroxide gels.

3. A process according to claim 1 or 2, wherein the hydroxylated polyalkene has a molecular weight of 950 to 10,000.

4. A process according to any one of the preceding claims, wherein the hydrophobic organic substance is a glycerol mono-, di- or tri-ester of palmitic or stearic acid.

5. A process according to any one of the preceding claims, wherein the hydrophobic organic substance is a hydrogenated mono-, di–or tri-glyceride in which 70 - 90 per cent by weight of the ester is 12-hydroxystearic ester and 10 - 30 per cent by weight of the ester is a stearic acid ester.

6. A process according to any one of the preceding claims, wherein the emulsifier is a polyoxyethylene-sorbitan mono-ester of an acid which is oleic, lauric, stearic or palmitic acid.

7. A process according to any one of the preceding claims additionally containing a gastric acid secretion

inhibitor.

8. A process according to claim 7, wherein the inhibitor is cimetidine, ranitidine or omeprazole.

9. A process according to any one of the preceding claims wherein the preparation is produced in the form of a powder, granulate or chewable tablet.

10. A process according to any one of the preceding claims wherein the emulsion is formed by dissolving the hydrophobic substance in an organic solvent, adding the emulsifier to the resulting solution and then emulsifying the hydroxylated polyalkene into the mixture of solution and emulsifier.

11. A process according to claim 10 wherein the emulsion contains 50 - 90 parts by weight of the hydrophobic substance and 10 - 20 parts by weight of the hydroxylated polyalkene, the balance being solvent and emulsifier.

12. A process according to any one of the preceding claims wherein 1 part by weight of the powder mixture is mixed and kneaded with 1 to 3 parts by weight of the emulsion, and a binder is then added to the resulting wet mass and the wet product finally granulated.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Festes pharmazeutisches Mittel mit einer Innenphase, die ein Pulvergemisch aus diskretem festem Granulat aus einem Antacidum und einem pharmazeutisch annehmbarem Trägerstoff bzw. Verdünnungsmittel ist, wobei die Innenphase von einer festen Außenphase umgeben ist, die eine hydrophobe organische Substanz, ein hydroxyliertes Polyalken und ein nichtionisches Emulgiermittel enthält.

2. Präparat nach Anspruch 1, dadurch **gekennzeichnet**, daß das Antacidum Almagat, Hydrotalcit, Magaldrat oder andere Aluminiumhydroxid- oder Aluminium-Magnesium-Hydroxid-Gele ist.

3. Präparat nach Anspruch 1 oder 2, dadurch **gekennzeichnet**, daß das hydroxylierte Polyalken ein Molekulargewicht von 950 bis 10000 aufweist.

4. Präparat nach einem der vorhergehenden Ansprüche, dadurch **gekennzeichnet**, daß die hydrophobe organische Substanz ein Glycerinmono-, -di- oder -triester von Palmitinsäure oder Stearinsäure ist.

5. Präparat nach einem der vorhergehenden Ansprüche, dadurch **gekennzeichnet**, daß die hydrophobe organische Substanz ein hydriertes Mono-, Di- oder Triglycerid ist, in dem 70 bis 90 Gew.-% des Esters ein 12-Hydroxystearinsäureester und 10 bis 30 Gew.-% des Esters ein Stearinsäureester ist.

6. Präparat nach einem der vorhergehenden Ansprüche, dadurch **gekennzeichnet**, daß das Emulgiermittel ein Polyoxyethylensorbitanmonoester einer Säure ist, die Öl-, Laurin-, Stearin- oder Palmitinsäure ist

7. Präparat nach einem der vorhergehenden Ansprüche, dadurch **gekennzeichnet**, daß es zusätzlich einen Magensäure-Sekretionsinhibitor enthält.

8. Präparat nach Anspruch 7, dadurch **gekennzeichnet**, daß der Inhibitor Cimetidin, Ranitidin oder Omeprazol ist.

9. Präparat nach einem der vorhergehenden Ansprüche, dadurch **gekennzeichnet**, daß es in Form eines Pulvers, Granulats oder einer kaubaren Tablette vorliegt.

10. Verfahren zur Herstellung eines Präparats nach einem der vorhergehenden Ansprüche, dadurch **gekennzeichnet**, daß eine Emulsion aus der hydrophoben organischen Substanz, dem hydroxylierten Polyalken und dem Emulgiermittel gebildet wird und daß das Pulvergemisch, das das Antacidum und den Arzneimittelträger enthält, mit der Emulsion granuliert wird.

11. Verfahren nach Anspruch 10, dadurch **gekennzeichnet** , daß die Emulsion durch Auflösen der hydropho-

ben Substanz in einem organischen Lösungsmittel, Zugabe des Emulgiermittels zu der entstehenden Lösung und dann Emulgieren des hydroxylierten Polyalkens in dem Gemisch aus Lösung und Emulgiermittel gebildet wird.

12. Verfahren nach Anspruch 11, dadurch **gekennzeichnet**, daß die Emulsion 50 bis 90 Gew.-Teile hydrophobe Substanz und 10 bis 20 Gew.-Teile hydroxyliertes Polyalken und als Rest Lösungsmittel und Emulgiermittel enthält.

13. Verfahren nach einem der Ansprüche 10 bis 12, dadurch **gekennzeichnet**, daß 1 Gew.-Teil Pulvergemisch mit 1 bis 3 Gew.-Teilen Emulsion vermischt und verknetet wird und daß dann ein Bindemittel zu der entstehenden naßen Masse zugegeben wird und daß das naße Produkt schließlich granuliert wird.

Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren zur Herstellung eines festen pharmazeutischen Mittels mit einer Innenphase, die ein Pulvergemisch aus diskretem festem Granulat eines Antacidums und eines pharmazeutisch annehmbaren Trägerstoffs bzw. Verdünnungsmittels ist, wobei die Innenphase von einer festen Außenphase umgeben ist, die eine hydrophobe organische Substanz, ein hydroxyliertes Polyalken und ein nichtionisches Emulgiermittel enthält, dadurch **gekennzeichnet**, daß eine Emulsion aus der hydrophoben organischen Substanz, dem hydroxylierten Polyalken und dem Emulgiermittel gebildet wird und daß dann ein Pulvergemisch, das das Antacidum und den Arzneimittelträgerstoff enthält, mit der Emulsion granuliert wird.

2. Verfahren nach Anspruch 1, dadurch **gekennzeichnet**, daß das Antacidum Almagat, Hydrotalcit, Magaldrat oder andere Aluminiumhydroxid- oder Aluminium-Magnesium-Hydroxid-Gele ist.

3. Verfahren nach Anspruch 1 oder 2, dadurch **gekennzeichnet**, daß das hydroxylierte Polyalken ein Molekulargewicht von 950 bis 10000 aufweist.

4. Verfahren nach einem der vorhergehenden Ansprüche, dadurch **gekennzeichnet**, daß die hydrophobe organische Substanz ein Glycerinmono-, -di- oder -triester von Palmitin- oder Stearinsäure ist.

5. Verfahren nach einem der vorhergehenden Ansprüche, dadurch **gekennzeichnet**, daß die hydrophobe organische Substanz ein hydriertes Mono-, Di- oder Triglycerid ist, in dem 70 bis 90 Gew.-% des Esters 12-Hydroxystearinsäureester und 10 bis 30 Gew.-% des Esters Stearinsäureester sind.

6. Verfahren nach einem der vorhergehenden Ansprüche, dadurch **gekennzeichnet**, daß das Emulgiermittel ein Polyoxyethylensorbitanmonoester einer Säure ist, die Öl-, Laurin-, Stearin- oder Palmitinsäure ist.

7. Verfahren nach einem der vorhergehenden Ansprüche, dadurch **gekennzeichnet**, daß zusätzlich ein Magensäure-Sekretionsinhibitor verwendet wird.

8. Verfahren nach Anspruch 7, dadurch **gekennzeichnet**, daß der Inhibitor Cimetidin, Ranitidin oder Omeprazol ist.

9. Verfahren nach einem der vorhergehenden Ansprüche, dadurch **gekennzeichnet**, daß das Präparat in Form eines Pulvers, Granulats oder einer kaubaren Tablette hergestellt wird.

10. Verfahren nach einem der vorhergehenden Ansprüche, dadurch **gekennzeichnet**, daß die Emulsion durch Auflösen einer hydrophoben Substanz in einem organischen Lösungsmittel, Zugabe des Emulgiermittels zu der entstehenden Lösung und dann Emulgieren des hydroxylierten Polyalkens in dem Gemisch aus Lösung und Emulgiermittel hergestellt wird.

11. Verfahren nach Anspruch 10, dadurch **gekennzeichnet**, daß die Emulsion 50 bis 90 Gew.-Teile hydrophobe Substanz und 10 bis 20 Gew.-Teile hydroxyliertes Polyalken enthält, wobei der Rest Lösungsmittel und Emulgiermittel ist.

12. Verfahren nach einem der vorhergehenden Ansprüche, dadurch **gekennzeichnet**, daß 1 Gew.-Teil Pulvergemisch mit 1 bis 3 Gew.-Teilen Emulsion vermischt und verknetet wird und daß ein Bindemittel zu der entstehenden nassen Masse zugegeben wird und daß das nasse Produkt schließlich granuliert wird.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Préparation pharmaceutique solide ayant une phase interne qui est un mélange pulvérulent de granules solides discrètes d'un antiacide et d'un excipient pharmaceutiquement acceptable, la phase interne étant entourée par une phase solide externe contenant une substance organique hydrophobe, un polyalcène hydroxylé et un émulsifiant non ionique.

2. Préparation selon la revendication 1, dans laquelle l'antiacide est l'Almagate, l'Hydrotalcite, le Malgaldrate ou d'autres gels à base d'hydroxyde d'aluminium ou d'hydroxyde d'aluminium et de magnésium.

3. Préparation selon la revendication 1 ou 2, dans laquelle le polyalcène hydroxylé présente une masse moléculaire de 950 à 10 000.

4. Préparation selon l'une quelconque des revendications précédentes, dans laquelle la substance organique hydrophobe est un mono-, di- ou triester glycérique de l'acide palmitique ou stéarique.

5. Préparation selon l'une quelconque des revendications précédentes, dans laquelle la substance organique hydrophobe est un mono-, di- ou triglycéride hydrogéné dans lequel 70-90 % en poids de l'ester sont constitués par un ester de l'acide 12-hydroxystéarique et 10-30 % en poids de l'ester sont constitués par un ester de l'acide stéarique.

6. Préparation selon l'une quelconque des revendications précédentes, dans laquelle l'émulsifiant est un monoester de polyoxyéthylène-sorbitan d'un acide qui est l'acide oléique, laurique, stéarique ou palmitique.

7. Préparation selon l'une quelconque des revendications précédentes, contenant en outre un inhibiteur de la sécrétion gastrique acide.

8. Préparation selon la revendication 7, dans laquelle l'inhibiteur est la cimétidine, la ranitidine ou l'oméprazole.

9. Préparation selon l'une quelconque des revendications précédentes, sous la forme d'une poudre, d'un granulé ou d'un comprimé mâchable.

10. Procédé pour la production d'une prépartion telle que définie dans l'une quelconque des revendications précédentes, qui comprend l'étape consistant à former une émulsion de la substance organique hydrophobe, du polyalkylène hydroxylé et de l'émulsifiant, et ensuite, à granuler un mélange en poudre contenant l'antiacide et l'excipient avec l'émulsion.

11. Procédé selon la revendication 10, dans lequel l'émulsion est formée par dissolution de la substance hydrophobe dans un solvant organique, addition de l'émulsifiant à la solution résultante et ensuite, émulsification du polyalkylène hydoxylé dans le mélange de solution et d'émulsifiant.

12. Procédé selon la revendication 11, dans lequel l'émulsion contient 50-90 parties en poids de la substance hydrophobe et 10-20 parties en poids du polyoxyalkylène hydroxylé, le reste étant constitué par le solvant et l'émulsifiant.

13. Procédé selon l'une quelconque des revendications 10 à 12, dans lequel 1 partie en poids du mélange de poudre est mélangé et malaxé avec 1 à 3 parties en poids de l'émulsion, et un liant est ensuite ajouté à la masse humide obtenue et enfin, le produit humide est granulé.

Revendications pour les Etats contractants suivants : ES, GR

1. Procédé de production d'une préparation pharmaceutique solide ayant une phase interne qui est une poudre mixte de granules solides discrètes d'un antiacide et d'un excipient pharmaceutiquement acceptable, la phase interne étant entourée par une phase solide externe contenant une substance organique hydrophobe, un polyalcène hydroxylé et un émulsifiant non ionique, qui comprend les étapes consistant à for-

mer une émulsion de la substance organique hydrophobe, du polyalkylène hydroxylé et de l'émulsifiant, et ensuite, à granuler un mélange en poudre contenant l'antiacide et l'excipient avec l'émulsion.

2. Procédé selon la revendication 1, dans lequel l'antiacide est l'Almagate, l'Hydrotalcite, le Magaldrate ou d'autres gels à base d'hydroxyde d'aluminium ou d'hydroxyde d'aluminium et de magnésium.

3. Procédé selon la revendication 1 ou 2, dans lequel le polyalcène Hydroxylé présente une masse moléculaire de 950 à 10 000.

4. Procédé selon l'une quelconque des revendications précédentes, dans lequel la substance organique hydrophobe est un mono-, di- ou triester glycérique de l'acide palmitique ou stéarique.

5. Procédé selon l'une quelconque des revendications précédentes, dans lequel la substance organique hydrophobe est un mono-, di- ou triglycéride hydrogéné dans lequel 70-90 % en poids de l'ester sont constitués par un ester de l'acide 12-hydroxystéarique et 10-30 % en poids de l'ester sont constitués par un ester de l'acide stéarique.

6. Procédé selon l'une quelconque des revendications précédentes, dans lequel l'émulsifiant est un monoester de polyoxyéthylène-sorbitan d'un acide qui est l'acide oléique, laurique, stéarique ou palmitique.

7. Procédé selon l'une quelconque des revendications précédentes, avec addition d'un inhibiteur de la sécrétion gastrique acide.

8. Procédé selon la revendication 7, dans lequel l'inhibiteur est la cimétidine, la ranitidine ou l'oméprazole.

9. Procédé selon l'une quelconque des revendications précédentes, dans lequel la préparation est mise sous la forme d'une poudre, d'un granulé ou de comprimés mâchables.

10. Procédé selon l'une quelconque des revendications précédentes, dans lequel l'émulsion est formée par dissolution de la substance hydrophobe dans un solvant organique, addition de l'émulsifiant à la solution résultante et ensuite, émulsification du polyalkylène hydroxylé dans le mélange de solution et d'émulsifiant.

11. Procédé selon la revendication 10, dans lequel l'émulsion contient 50-90 parties en poids de la substance hydrophobe et 10-20 parties en poids du polyoxyalkylène hydroxylé, le reste étant constitué par le solvant et l'émulsifiant.

12. Procédé selon l'une quelconque des revendications précédentes, dans lequel 1 partie en poids du mélange de poudre est mélangé et malaxé avec 1 à 3 parties en poids de l'émulsion, et un liant est ensuite ajouté à la masse humide obtenue et enfin, le produit humide est granulé.